CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE BRIEFING DOCUMENT

December 8, 2010

Bypass Graft Failure as a Clinical Endpoint for CABG Patients

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ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
ACS	Acute coronary syndrome
ACC	American College of Cardiology
ACCP	American Cardiology Chest Physicians
AHA	American Heart Association
AMI	Acute Myocardial Infarction
ASA	Aspirin
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CI	Confidence Interval
CT	Computed tomography
CVD	Cardiovascular disease
EACTS	European School For Cardio-Thoracic Surgery
EF	Ejection Franction
ESC	European Society of Cardiology
FDA	Food and Drug Administration
ICA	Invasive coronary angiography
MACE	Major adverse cardiac event
MDCT	Multi detector computed tomography
MI	Myocardial infarction
OR	Odds ratio
PCI	Percutaneous coronary intervention
RCT	Randomized controlled trial
RR	Relative risk
SPECT	Single photon emission computed tomography
STS	Society of Thoracic Surgeons
SVG	Saphenous Vein Graft

1. EXECUTIVE SUMMARY

Coronary artery disease (CAD) is the leading cause of mortality in the United States in men and women of every major ethnic group. Coronary artery bypass grafting (CABG) is an effective therapy performed on ~450,000 patients per year in the USA. The primary intention of this procedure is to relieve symptoms of CAD and, in certain subgroups, to prolong survival, both of which are presumably accomplished by establishing widely patent bypass grafts to myocardium that is poorly perfused due to CAD in native vessels. Consistent with this hypothesis, clinical data suggest that the more complete a patient is revascularized (i.e., the more bypass grafts they receive) the better their outcomes. As a consequence of a variety of factors including surgical technique/conduit preparation and factors intrinsic to the procedure and patient, however, it is common for these conduits to fail (i.e., become occluded). Bypass graft failure has been shown in a number of studies to be independently correlated with a variety of adverse clinical outcomes including death, myocardial infarction, revascularization, and worsening of symptoms such as angina.

The early failure of bypass grafts is due predominantly to platelet-mediated occlusion caused by increased thrombogenicity within the grafted vessel, a phenomenon attributed to surgical manipulation, distension of the isolated vein before anastomosis and reduced antithrombogenic properties of the endothelium. Late graft failure occurring ≥ 1 year post-surgery, by contrast, has been associated with inflammation and atherogenesis although it still includes a component of thrombosis that can occlude a narrowed but otherwise functioning graft. Because a significant contributor to bypass graft failure is thrombosis, the anti-thrombotic agent aspirin has proven to be effective in maintaining bypass graft patency and this is the primary reason cited for the peri- and post-operative use of aspirin in all major cardiovascular/cardiothoracic societies' guidelines.

While the correlation between graft failure and other adverse outcomes is known to exist, there is regulatory uncertainty as to the strength of this relationship and its causal role. Finally, new modalities of assessing bypass graft anatomy such as computed tomography (CT) angiograms now exist and are reported to have equal effectiveness in assessing bypass graft anatomy, but this new modality's role in assessing graft anatomy in the context of endpoints in clinical trials is not well defined.

Thus the intentions of this document are to further explore:

- the benefits of CABG
- graft failure and its relationship with outcomes
- aspirin's role in the prevention of graft failure
- CT angiography as an acceptable modality for assessing bypass graft failure.

2. CORONARY ARTERY BYPASS GRAFTING (CABG)

2.1 CABG USAGE AND GRAFT PATENCY

Coronary artery disease (CAD) is the leading cause of mortality in the United States in men and women of every major ethnic group. For nearly half a century, coronary artery bypass grafting has been a standard procedure for the revascularization of the myocardium that is compromised by CAD and is currently performed in the United States approximately 450,000 times per year (448,000 were performed in 2006 - the Americanheart.org, Statistics Heart Disease and Stroke 2010 updates). CABG has proven to be an effective means of decreasing symptoms of CAD and has also been associated with control of symptoms and a mortality benefit extending out to 10 years compared to patients treated with medical therapy (Yusuf, Zucker et al. 1994) (**Table 1**).

Table 1: CABG Improves Long Term Survival

Trial	No. of Patients Randomized		5-Year Mortality			10-Year Mortality		
	CABG	Medical Treatment	CABG	Medical Treatment	Odds Ratio (95% CI)	CABG	Medical Treatment	Odds Ratio (95% CI)
VA (79)	332	354	58	79	0.74 (0.50–1.08)	118	141	0.83 (0.61–1.14)
European (81)	394	373	30	63	0.40 (0.26–0.64)	91	109	0.72 (0.52–0.99)
CASS (80)	390	390	20	32	0.60 (0.34–1.08)	72	83	0.84 (0.59–1.19)
Texas	56	60	10	13	0.79 (0.31–1.97)	23	25	0.97 (0.46–2.04)
Oregon	51	49	4	8	0.44 (0.12–1.56)	14	14	0.94 (0.39–2.26)
New Zealand	51	49	5	7	0.65 (0.19–2.20)	15	16	0.94 (0.38–2.31)
New Zealand	50	50	8	8	1.00 (0.34–2.91)	17	16	1.15 (0.50–2.65)
Total	1324	1325	135	210	0.61 (0.48–0.77)	350	404	0.83 (0.70–0.98)
			(10.2%)	(15.8 %)	P less than 0.0001	(26.4 %)	(30.5 %)	P equals 0.03

CABG indicates coronary artery bypass graft; CI, confidence interval; VA, Veterans Administration; CASS, Coronary Artery Surgery Study.
P values for heterogeneity across studies were 0.49, 0.84, and 0.95 at 5, 7, and 10 years, respectively. Reprinted with permission from Elsevier Science, Inc. (Yusuf et al. The Lancet 1994;344:563-70) (85).

The benefit of CABG has been most clear in patients with left main or left main equivalent coronary artery disease, multi-vessel CAD, and those with more severe anginal symptoms (Yusuf, Zucker et al. 1994)

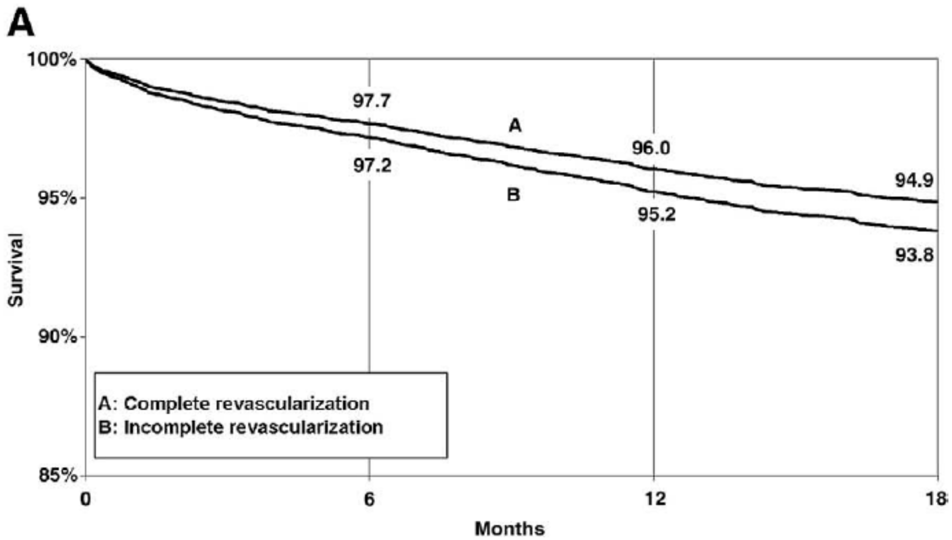
The benefits of CABG accrue from the re-establishment of adequate blood flow to the myocardium by conduits (grafts) that bypass obstructions in the coronary arteries. Consistent with this hypothesis is the observation that more complete revascularization is associated with improved outcomes as suggested by Sarno et al. (Sarno, Garg et al.), who reported on outcomes in 567 patients who underwent CABG and who received complete as compared to incomplete revascularization, as assessed by grafting of all vessels with >50% stenoses in each of the main and side branches of the coronary arteries. They observed fewer death/strokes/MIs/any revascularization at 5 years in CABG patients who were completely revascularized (19.7%) vs. incompletely revascularized (21.1%). Similar findings were reported in the 3372 patient Coronary Artery Surgical Study (CASS) Registry (Bell, Gersh et al. 1992) (**Table 2**). The study suggested benefits in improved survival and better control of symptoms in patients with severe angina who received more complete revascularization (as defined by placement of ≥3 grafts) as compared to incomplete (≤2 grafts) revascularization in patients with severe angina:

Table 2: 4-6 Year Survival Rates in Patients with 3 Vessel CAD—CASS Registry (N= 3372)

	1 vessel CABG	2 vessel CABG	≥3 vessel CABG	p value
Class 1 or 2 angina	85%	94%	96%	p<0.02
Class 3 or 4 angina	78%	85%	≥87%	p<0.07
EF < .35 + Class 3 or 4 angina		45%	69%	p<0.04

Also consistent with the hypothesis that improved blood flow also improves outcomes were the findings of Hannan et al, who reported statistically significant (p=0.01) improvement in survival in patients completely revascularized via percutaneous interventions vs. incompletely revascularized via percutaneous interventions (Hannan, Wu et al. 2009)(**Figure 1**).

Figure 1: Improved Survival with Complete Revascularization



2.2 BYPASS GRAFT FAILURE

The improvement of blood flow by CABG and by more complete revascularization has been observed to correlate with improved outcomes, so too has it been observed that decreases in blood flow, as manifest by bypass graft failure (occlusion), are correlated with worse outcomes. This is due to either a reduction in blood flow or distal embolization of thrombi into smaller downstream native coronary vessels. The early occlusion of bypass grafts is due predominantly to platelet-mediated occlusion caused by increased thrombogenicity within the grafted vessel, a phenomenon attributed to surgical manipulation, distension of the isolated vein before anastomosis and reduced antithrombogenic properties of the endothelium. Graft failure occurring 1-6 months post-CABG is thought to be mediated by intimal hyperplasia and thrombosis. Late graft failure occurring ≥ 1 year post-surgery, by contrast, has been associated with inflammation and atherogenesis although it still includes a component of thrombosis that can occlude a narrowed but otherwise functioning graft (1994; Motwani and Topol 1998; Li, Astudillo et al. 2003). Bypass graft failure is unfortunately quite common with per patient rates of ~42% observed at 1 year in a contemporary CABG trial using optimal medical therapy, including aspirin (Alexander, Hafley et al. 2005).

Halabi et al. (Halabi, Alexander et al. 2005) made the observation of worse outcomes correlating with extent of bypass graft disease/failure when they examined clinical outcomes from the Duke Cardiovascular Databank for 1,243 patients who underwent diagnostic angiography from 1 to 18 months after their first CABG procedure. They classified patients according to categorical degree of bypass graft disease and determined the incidence of MI that had occurred prior to angiography as follows (**Table 3**):

Table 3: Clinical Events (Death, MI or Revascularization) Occurring Before Angiography by Bypass Graft Status[1]

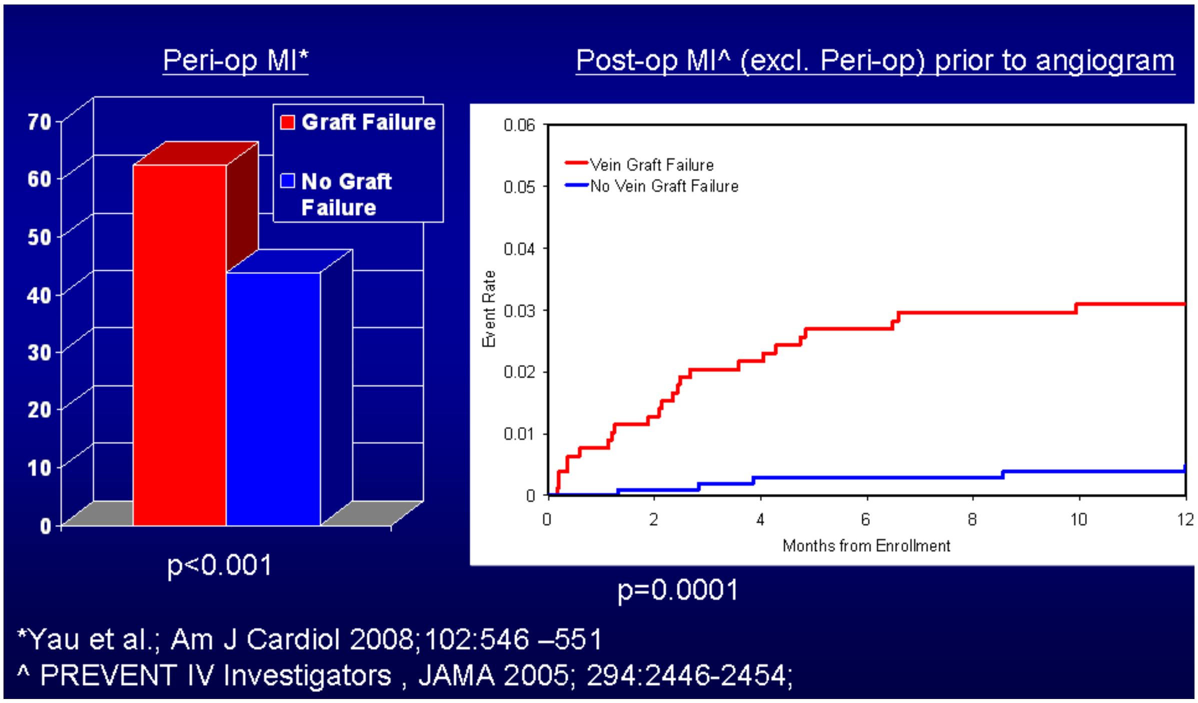
Degree of Bypass Graft Disease (% Stenosis)	% Stenosis	Proportion of Cohort	Incidence of MI Post-CABG to Angiography
None	< 25%	27.9%	7.8%
Noncritical	25% or 50%	11.9%	8.8%
Critical	75% or 95%	20.8%	10.8%
Occlusive	100%	**2.2.1** 39.3%	**2.2.2** 19.0%

2.2.3 1. (Halabi, Alexander et al. 2005)

Patients were also followed after angiography for MACE. A multivariate analysis identified critical saphenous vein graft (SVG) disease and the number of bypass grafts with either critical or occlusive disease as significant independent predictors of subsequent MACE ($p<0.0001$ for both covariates). Angiographic bypass graft disease was not identified as an independent predictor of mortality in this trial, however.

Similarly, in the PREVENT IV study, bypass graft failure was statistically significantly correlated with both perioperative MIs (62.4% vs. 43.8%; $P<0.001$; (Yau, Alexander et al. 2008) and post-operative MIs, excluding peri-op MIs, occurring up to the time of angiogram ($p<0.0001$)(**Figure 2**).

Figure 2: Peri Operative and Post Operative Myocardial Infarctions Correlated with Graft Failure



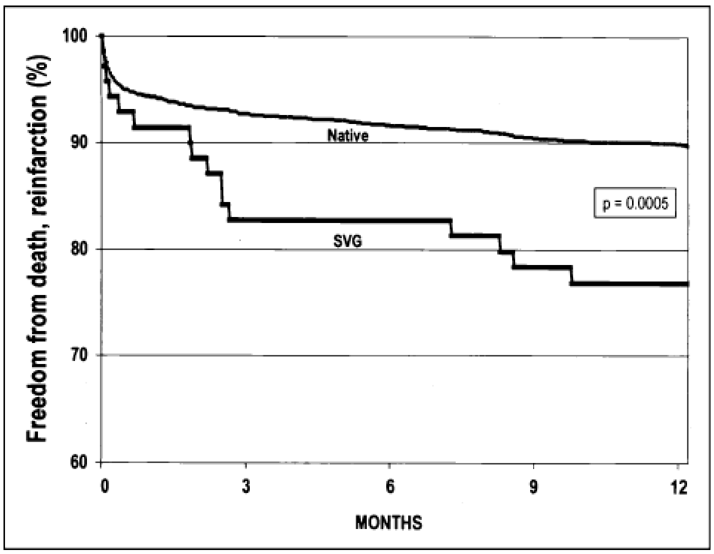
Further underscoring the importance of patent bypass grafts, Lichtenwalter et al. observed that, among 80 patients undergoing percutaneous coronary intervention (PCI) and stenting of a saphenous vein bypass graft, 30% of those patients who experienced subsequent stent failures presented as acute myocardial infarctions (Lichtenwalter, de Lemos et al. 2009), suggesting the myocardium perfused by the bypass grafts was critically dependent on that additional blood flow.

Also consistent with this observation was that made by Al Suwaidi et al (Al Suwaidi, Velianou et al. 2001), who reported on a series of 128 post-CABG patients who underwent primary PCI for AMI. Sixty-five of the patients had a native coronary artery as the target vessel, while 63 had a bypass graft. They found that grafts were associated with a higher risk of distal coronary embolization (9.4% vs. 4.1%, p=0.009), MACE (RR 1.48; 95% CI 1.07-2.03; P=0.02) and death (RR 1.74; 95% CI 1.16-2.61; P=0.008).

More recently, Abdel-karim (Abdel-Karim, Banerjee et al. 2010) has reported a series of 34 patients who underwent PCI for acutely occluded bypass grafts who experienced a strikingly high rate of subsequent events, including stent thrombosis in 41% and mortality rates of 8% and 42% at 1 and 3 years, respectively, suggesting the critical nature of the blood flow provided by bypass grafts.

Nguyen et al (Nguyen, O'Neill et al. 2003) found that in post-CABG patients undergoing primary angioplasty for acute myocardial infarction there was a statistically significant increase in the composite endpoint of death or reinfarction when the culprit lesion was a saphenous vein bypass graft and not a native vessel (**Figure 3**):

Figure 3: Kaplan-Meier curve for Freedom from Death and Reinfarction After Primary Angioplasty for AMI



Note: Event rates are stratified by the type of culprit vessel.

The 1 year mortality observed in SVG vs. native culprit lesions was 20% vs. 6.3% ($p < 0.001$), respectively, again suggesting loss of bypass grafts is more negatively prognostic than deterioration of native vessel disease.

Clinical data also suggest that bypass graft status is correlated with CAD symptoms. For example, Assad-Morell et al.(Assad-Morell, Frye et al. 1975) from the Mayo Clinic reported the results of a cohort of 500 consecutive patients that underwent CABG with subsequent outcomes according to the number of stenosed native coronary arteries (defined as a > 50% stenosis) that were left ungrafted. Briefly, they noted that patients with more complete revascularization were less symptomatic at both 1 (**Table 4**) and 3 (**Table 5**) years after their procedure.

Table 4: Clinical Results, by Number of Vessels Left Ungrafted (VLU): 1 to 12 Months Postoperatively

	No VLU	One VLU	Two VLU	Three VLU
Total patients (no.)	20	50	24	6
Pain-free (no.)	17 (85%)	26 (52%)	5 (21%)	1 (17%)
Improved (no.)	0	10 (20%)	8 (33%)	2 (33%)
Unimproved (no.)	3 (15%)	14 (28%)	11 (46%)	3 (50%)

Table 5: Clinical Results, by Number of Vessels Left Ungrafted (VLU): 1 to 3 Years Postoperatively

	No VLU	One VLU	Two VLU	Three VLU
Total patients (no.)	26	19	13	4
Pain-free (no.)	21 (80%)	12 (63%)	2 (16%)	0
Improved (no.)	5 (20%)	7 (37%)	3 (23%)	2 (50%)
Unimproved (no.)	0	0	8 (61%)	2 (50%)

Similarly, Anderson et al (Anderson, Rahimtoola et al. 1974) reported a series of 532 CABG patients who were studied by angiography and related their graft status to New York Heart Association Functional Classification (**Table 6**). Briefly, classification III and IV was relatively uncommon in patients with either no occluded or both patent and occluded grafts, whereas patients with all occluded grafts were quite likely to have advanced, symptomatic heart failure in stage III or IV.

Table 6: New York Heart Association Functional Classification by Graft Status

	Functional classification (no. patients)		
	I	II	III & IV
Patients studied			
All grafts patent	65	63	4
Both patent and occluded grafts	18	11	5
All grafts occluded	5	9	11
Total patients studied	88	83	20
Patients not studied	199	95	15

*Deaths and losses to follow-up are excluded and removals for cause (reoperations) are tallied as treatment failures (FC III & IV).

While there is clearly a correlation between bypass graft failure and adverse outcomes including MI, MACE, and symptoms, Portola acknowledges there are difficulties in trying to link individual graft failures to outcomes. Nonetheless, the above described evidence supports the concept that preventing graft failure after CABG surgery is in itself a worthwhile clinical goal and that it should result in a lower risk of MACE.

2.3 ASPIRIN REDUCES THE RISK OF GRAFT FAILURE AND IMPROVES OUTCOMES IN CABG PATIENTS

The antithrombotic effectiveness of aspirin therapy both before and after CABG procedures has been studied extensively and demonstrated in clinical trials. The beneficial effect of aspirin in preventing graft failure has been recognized for many years (Chesebro, Fuster et al. 1984; Lorenz, Schacky et al. 1984). In addition to its beneficial effects in preventing graft failure, aspirin use after CABG has been linked with decreased mortality in two large observational series. Dacey et al (Dacey, Munoz et al. 2000) reported an odds ratio of 0.73 (CI 0.52 -0.97) for in-hospital mortality in a case-controlled series of 8,641 patients who received aspirin at the time of CABG surgery as compared to those who had not. Mangano confirmed and extended these observations in a longitudinal series of 5,065 patients on whom 7,500 data points per patient were gathered (Mangano 2002). In this series, a relative reduction in in-hospital mortality of 67% (4.0% vs. 1.3%, $p<0.001$) was reported in patients who received aspirin within 48 hours after their procedure. In addition to the mortality benefit, patients who received aspirin experienced a 48% reduction in MI, a 50% reduction in stroke, a 74% reduction in the incidence of renal failure and a 62% reduction in the incidence of bowel infarction as compared to patients who did not receive aspirin. Although this was not a randomized study, an extensive multivariate analysis was performed that showed the association of these outcomes with aspirin after adjusting for other factors and/or medications.

In view of these data, aspirin is commonly used preoperatively and its use immediately (≤48 hours) after CABG has been accorded a Class I recommendation for the maintenance of graft patency in the treatment guidelines of all of the major Western cardiology/thoracic surgery societies [ACCP 2008; AHA/ACC 2005; STS 2003; ESC 2010; EACTS 2008 (Stein, Schunemann et al. 2004)].

2.4 USE OF CT ANGIOGRAPHY TO ASSESS BYPASS GRAFT FAILURE

To date, invasive coronary angiography (ICA) has been the gold standard in defining coronary artery anatomy, including the status of coronary bypass grafts. However, this invasive procedure is associated with infrequent, but significant complications including renal failure, bleeding, MI, stroke, and death (Gobel, Stewart et al. 1998). Sixty-four slice CT angiography, a non-invasive alternative to ICA, has now come into common usage and offers the advantage of a lower risk of bleeding and thrombotic complications. CT angiography has been compared directly to ICA in multiple studies and it has consistently been demonstrated to detect occlusions in bypass grafts with comparable ability (i.e., sensitivity and specificity values generally ≥90%) to ICA (Jones, Athanasiou et al. 2007) and, at least in a symptomatic CAD population, with negative and positive predictive values ≥93% (Meyer, Martinoff et al. 2007). It is therefore Portola's position that 64 slice CT angiography is an acceptable means of determining bypass graft anatomy in clinical trials in CABG.

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